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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,287	10/08/2003	G. Roger Askew	47038.0179/00US	5825

55694 7590 09/07/2007

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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	
MAIL DATE	**DELIVERY MODE**
09/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/680,287	ASKEW ET AL.
	Examiner	Art Unit
	Joanne Hama, Ph.D.	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-13 and 45-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-13 and 45-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 12, 2007 has been entered. Claims 10, 14-44, 48 are cancelled. Claims 1, 2, 4, 12, 46 are amended.

Claims 1-9, 11-13, 45-47 are under consideration.

Information Disclosure Statement

Applicant filed an Information Disclosure Statement (IDS) on June 12, 2007. The IDS has been considered.

Applicant indicates that copies of Corseaux et al., 2002 and Schneider et al., 1994 have been submitted in Applicant's response dated November 11, 2004. The references had been stricken from the PTO-1449 that had been submitted January 16, 2004. In response, the Examiner has acknowledged the receipt of Corseaux et al. and Schneider et al., submitted by Applicant, November, 2005, in the January 27, 2006 Office Action, page 2. It is also noted that the Examiner has initialed the IDS filed by Applicant on November 8, 2005 and indicated that Corseaux et al. and Schneider et al. have been considered.

Withdrawn Rejections

Double Patenting

Applicant's arguments, see pages 5-6 of Applicant's response, filed June 12, 2007, with respect to the provisional rejection of claims 1-9, 11-13, 45-47 as being unpatentable over claims 1-3, 5-8, 10-14, 16 of U.S. Patent Application No. 10/477,238 ('238) have been fully considered and are persuasive. Applicant indicates that claims 1-3, 12, 14 of '238 have been cancelled. The provisional rejection of claims 1-9, 11-13, 45-47 has been withdrawn.

35 U.S.C. § 112, first parag., Written Description

Applicant's arguments, see page 6 of Applicant's response, filed June 12, 2007, with respect to the rejection of claims 1-9, 11-13, 45-47 have been fully considered and are persuasive. Applicant indicates that the claims have been amended and no longer refer to a "homolog." The claims have been amended to a mouse LRP5 protein having a glycine 170 to valine substitution. The rejection of claims 1-9, 11-13, 45-47 has been withdrawn.

Maintained Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11-13, 45-47 remain rejected in modified form under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a transgenic mouse comprising in its genome, a transgene construct comprising SEQ ID NO. 4 operably linked to a CMVbActin or rat type I collagen promoter, wherein said transgenic mouse has increased bone density,

does not reasonably provide enablement for

a transgenic mouse having somatic and germ cells comprising a nucleic acid which comprises any promoter region that directs protein expression in said transgenic mouse cells that is operably linked to a sequence encoding SEQ ID NO. 4 or a sequence encoding a mouse LRP5 protein having a glycine 170 to valine substitution, and wherein said transgenic mouse has increased bone density.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for reasons of record, June 9, 2005 and January 27, 2006.

Upon further consideration, new issues of enablement are addressed as follows. Response to Applicant's rebuttals, filed June 12, 2007 follow the new issues of rejection.

The claims are drawn to a transgenic mouse having somatic and germ cells comprising a nucleic acid which comprises a promoter operably linked to SEQ ID NO. 4 or a nucleic acid that encodes a mouse LRP5 protein having a glycine 170 to valine substitution, wherein said mouse exhibits increased bone density.

The claims are drawn to the use of any promoter. There are three issues at hand with regard to the use of any promoter. First, any promoter encompasses tissue-specific promoters that are not expressed in bone, such as muscle-specific, or skin-specific promoters. According to the specification and art, LRP5 is a receptor and that its role in accruing bone mass occurs in bone (e.g. see Gong et al., 2001, Cell 107: 513-523, see IDS). The claims broadly read as though expression of LRP5 in tissues other than bone (e.g. cartilage or muscle) would result in the bone mass phenotype. However, neither the art nor specification provide guidance that LRP5 or HBM expressed in other tissue (such as muscle or skin) results in transgenic mice that exhibit an increased bone mass. As such, the claimed invention is limited such that the phenotype occurs when the transgene construct is expressed in bone.

The second issue is that with regard to the scope of bone-specific promoters, the art teaches that there is unpredictability in using tissue-specific promoters from heterologous animals. For example, Cowan et al. 2003, Xenotransplantation, 10: 223-231, see IDS, teach that promoters of three human genes, ICAM-2, hCRPs, and PECAM-1, are predominantly expressed in vascular endothelium in mice and pigs. When tissue specific expression was measured, it was found that while mice showed a distinct expression profile of the three human genes, the tissue expression profiles of the three human gene promoters were distinctly different in pigs. The authors concluded that "promoter performance in mice and pigs was not equivalent," and that "the weak expression driven by the human ICAM-2 promoter in pigs relative to mice suggests the need for additional regulatory elements to achieve species-specific gene expression in pigs (Cowan et al., abstract)." Cowan et al.'s teaching indicates that an artisan cannot reasonably predict that tissue-specific promoters behave predictably in transgenic animals. While the specification teaches that a rat type I collagen promoter was used to express HBM in transgenic mice (specification, pages 158 and 171) the specification does not provide guidance that bone-specific promoters from heterologous species of animals can be used to arrive at the claimed invention. As such, the claims are limited to rat type I collage promoter.

The third issue with regard to the scope of promoter has to do with the predictability of promoter activity such that a phenotype is exhibited in the claimed mice. The art teaches that various promoters have varying ability to drive transgene expression in various cell types, in vivo. Xu et al., 2001, Gene 272: 149-156 teach that there are differences in promoter activity of ubiquitous promoters. Further, there are differences of promoter activity in different cell types in vivo (Xu et al., Figure 1B). As this issue applies to the instant invention, the claims encompass the use of any promoter. However the specification does not teach an artisan that the claimed invention could be practiced with a wide variety of promoters, particularly those that express at low levels. It is noted that while Xu et al. teach ubiquitous promoters, the same issue applies to bone-specific promoters. While the specification teaches that CMVbActin and rat type I collagenase promoters could be used to generate the mice described in the specification, pages 171-172, the specification does not provide guidance that other promoters can drive expression of HBM, such that the mice exhibit the phenotypes described in the specification. As such, the claims are enabled for CMVbActin and rat type I collagenase.

The claims are drawn to the use of SEQ ID NO. 4 (human HBM protein) or a mouse LRP5 protein having a glycine 170 to valine substitution. At the time of filing, the art teaches that an artisan cannot predict that the phenotype exhibited by a transgenic mouse overexpressing human protein would necessarily result in the same phenotype as a transgenic mouse overexpressing the mouse protein. For example, Vaisman et al., 2001, J. Clinical Investigation, 108: 303-309 teach that there are differences in in vivo function of LCAT in transgenic mice that overexpress the mouse versus the human protein (Vaisman et al., page 308, 1st col., 1st parag.). As such, an artisan cannot reasonably predict that mouse proteins necessarily have the same activity of a human protein in transgenic animals. Thus, the claim is enabled only for human HBM protein.

The claims are drawn to transgenic rodents that exhibit bone mass modulation (e.g. see claim 2). "Modulation" encompasses increases and decreases in bone mass. Nothing in the specification teaches an artisan how to arrive at transgenic rodents that overexpress HBM and exhibit decreased bone mass and thus, the specification does not provide support for the full breadth of the claims.

Applicant's arguments filed June 12, 2007 have been fully considered and they are persuasive in part.

Applicant indicates that the rejection of all the claims apparently is maintained because of the rejection of the term "homolog" in the claims. The Office asserts that it is unclear what characteristics are used to arrive at a mouse homolog. Applicant indicates that the term "homolog" is not recited in the text. In response, the deletion of the term "homolog" overcomes the issue of scope of proteins from heterologous animals encompassed by the term (Applicant's response, page 7). In this respect, the rejection of the claims is withdrawn. However, it is noted above that the specification does not provide guidance to use a mouse LRP5 protein having a glycine 170 to valine substitution. See above for further discussion. As such, the claims are rejected in this respect.

With regard to the issue of the claims not reciting a phenotype (see Office Action, July 18, 2006, page 13), it is noted that in the claim amendments filed October 17, 2006, that the claims (e.g. claims 2 and 46) have been amended to indicate that the claimed mice exhibit a phenotype. As such, the rejection as it applies to this issue is withdrawn.

With regard to the claims being drawn to a transgenic mouse, wherein the mouse comprises an episomal construct, and wherein the transgene construct is not stably integrated in the mouse's genome (Office Action,.July 18, 2006, page 14), Applicant has not addressed this issue. As such, the rejection as it applies to this issue remains. To illustrate the issue of enablement further with regard to this issue, the Examiner turns to the teachings of the art that illustrate to problems with using non-integrated constructs in transgenic animals. Smith teaches that episomal vectors (e.g. plasmid vectors) behave in an unstable fashion. During development, plasmid copy numbers fluctuate and plasmids are lost from cells (Smith, 2004, Int. J. Med. Sci., 1: 76-91, see IDS, page 83, under "5. Episomal Vectors"). The art also teaches that unintegrated copies of the microinjected transgene are degraded within four to five days (Page et al., 1995, Transgenic Research, 4: 12-17, see IDS, page 16, 1st col., 2nd parag. under "Discussion"). As these teachings apply to the instant invention, an artisan cannot predictably practice the claimed invention using episomal vectors.

The claims encompass transgenic rodents that comprise a transgene not stably integrated in the genome also indicates that the rodents are readable on methods using steps like that of gene therapy. The art teaches that there are problems with using vectors to deliver a gene of interest during gene therapy. In the case of a plasmid (non-viral) vector, while they do not raise immune response (Abdallah et al., 1995, Biol. Cell., 85: 1-7, see IDS, page 1, 2nd col., 3rd parag.), as the viral vectors do, they suffer from inefficient gene transfer (Somia and Verma, 2000, Nature Reviews: Genetics, 1: 91-99, see IDS, page 91, 1st col., 2nd parag.). The art teaches that using a viral vector as a vehicle to deliver a nucleic acid of interest is unpredictable. These issues of unpredictability include immune responses to the transgene product, the dose of virus administered, the promoter chosen to drive expression of the recombinant gene, the innate immune mechanisms and direct cytotoxcity cause by expression of viral genes (Somia and Verma, page 92, Box 1). In addition to this, while an adenoviral vector remains episomal, and expresses a transgene transiently, some viral vectors, such as retroviral, lentiviral, and adeno-associated viral, will integrate into the genome and express for life-long expression of the transgene (Somia and Verma, page 91, 2nd col., 2nd parag.). However, one major problem with viral vectors that they integrate in the host's genome is that the integration is random. In addition to the problem of random integration being that transcription of the transgene may then become under the control of neighboring factors of the host genome, the problem with random integration is that the transgene may integrate and disrupt a vital gene (Somia and Verma, page 93, 2nd col., 1st parag., see also, page 92, Box 1). As these issues relate to the claimed invention, nothing in the specification provide any guidance that any vector can be used to generate a transgenic animal, such that the transgenic animal exhibits a bone phenotype. As such, because the specification does not provide guidance to overcome the problems associated with viral vectors, an artisan is not enabled for any vectors.

Another problem associated with gene therapy is delivery. The art teaches that,

> "in order for a carrier system to preferentially accumulate at sites of systemic disease, such as tumors, sites of inflammation, and sites of infection, the carrier must exhibit long circulation lifetimes following intravenous injection. Unfortunately, most gene delivery systems including viral vectors as well as non-viral vectors, e.g., lipoplexes, polyplexes, and lipopolyplexes, are rapidly cleared from the circulation and are preferentially taken up by the 'first-pass' organs such as liver, lung, and spleen (Fenske, et al., 2001, Current Opinion in Molecular Therapeutics, 3: 153-158, see IDS, see abstract)."

As this situation applies to the instant invention, nothing in the specification provides guidance as to how to administer a vector comprising a nucleic acid sequence encoding HBM or a mouse LRP5 protein having a glycine 170 to valine substitution, such that the vector arrives at the bone cells, expresses HBM or a mouse LRP5 protein having a glycine 170 to valine substitution, and effects a bone phenotype. It is noted that the vector has to arrive at bone cells because HBM or a mouse LRP5 protein having a glycine 170 to valine substitution is a receptor and is not a diffusible protein. As such, the specification does not provide guidance for an artisan to practice the claimed invention for an episomal vector.

The claims read on a transgenic rodent comprising transplant, wherein the transplant comprises cells with a transgene construct. At the time of filing, the art teaches that cell and organ transplantation is unpredictable. With regard to a xenogeneic or allogeneic transplant, one major problem associated with these transplants is loss or rejection of the cell. The loss or rejection stems from an immune response to the foreign cell (Platt, 1998, Nature, 392 supplement: 11-17, see IDS; page 11, 2nd col. under "The barriers to xenotransplantation". While one might use drugs to immunosuppress a host, the specification does not teach what those drugs may be nor does the specification teach how to administer such drugs (which drugs, how much, route of delivery, for what duration of time). In addition to this, a skilled artisan would need to know how to prevent infection of the host organism, while the host's immune system is suppressed (Platt, page 14, Box 1, 1st parag.). One may suggest that syngeneic cells could be used to circumvent the problem with cell rejection. Certainly, this is a possibility as Gage teaches that syngeneic cells need not integrate into a homotypic region (Gage, 1998, Nature, 392 supplement, pages 18-24, see IDS; page 18, 2nd col., 1st parag. under "Function of cells as implants"). However, if long-term survival is required, success of the graft appears to depend on the cell type, the site of implantation, and type or class of promoter (Gage, page 19, 1st col., lines 2-5). Alternatively, if in the cases that require a cell to integrate into a homotypic region and perform specific physiological roles, a skilled artisan would need to know the phenotype of the cell and the spatial location critical to its utility (e.g. a retinal cell transplant or a skin graft) (Gage, page 19, 1st col., 2nd parag. to 2nd col., 2nd parag.). In addition to selecting a cell, a skilled artisan would need to consider that the transplanted cell would be comprised of a DNA expression vector. The art teaches that sometimes following transplantation, a cell comprised of a transgene may alter its level of transgene expression. For example, Fisher teaches that a neuronal cell line, RN33B, show loss of β-gal labeling in cells grafted in the CNS. The change in gene expression does not appear to be because the skilled artisan used a retrovirus. Gene expression is also compromised in cells wherein adenovirus or herpes virus vectors were used (Fisher, 1997, Neurobiology of Disease, 4: 1-22, see IDS; page 15, 2nd col., 2nd parag. under "In vivo considerations of genetically modified cells," lines 1-13). Thus, for reasons described above, a xenogenic or allogeneic transplant of faces the problem of host rejection. The methods involved to reduce the chance of rejection would need to be empirically determined. Coupled with this, to reduce rejection may involve methods of reducing infection in the host. This, too, would need to be empirically determined. In the case of syngeneic cells, a skilled artisan would need to be taught what kind of cells would need to be isolated, how to isolate said cells, and how to culture said cells. This would need to be empirically determined. Finally, whether a transgene construct can be reliably expressed would also need to be considered. Thus, for the reasons described above with regard to cell transplantation, the specification as filed does not provide sufficient guidance, working examples and evidence as to how an artisan of skill would have made and used the claimed invention commensurate with the scope of the claims without undue experimentation.

As such, the claims are rejected.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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